REMARKS

Claims 46-53, 55-69, 71, and 72 are pending in the case. Claims 62-69, 71, and 72 were withdrawn from consideration, pursuant to a Restriction Requirement, leaving claims 46-53 and 55-61 subject to further examination. Claims 46-51 remain provisionally rejected under the judicially-created Doctrine of Obviousness-Type Double Patenting, and claims 46-53 and 55-61 remain rejected under 35 U.S.C. § 103(a). The rejections are addressed below.

First, Applicants would like to thank the Examiner for the helpful interview concerning this case on April 30, 2007. Proposed amendments were discussed during the interview, including amending the claims to specify particular sequences, as set forth in the amendment set forth above. Applicants respectfully request consideration of these amendments.

Double Patenting

Claims 46-51 remain provisionally rejected under the judicially-created Doctrine of Obviousness-Type Double Patenting over claims 1, 4, 8, and 10 of U.S. Serial No. 10/895,646. When the only rejection remaining in a case is a provisional double patenting rejection, an application should be allowed to issue. M.P.E.P. § 822.01. In view of the amendments and remarks provided herein, Applicants submit that all of the grounds of rejection in this case, other than the provisional double patenting rejection, have been met. Accordingly, the provisional double patenting rejection should be withdrawn and the case allowed to issue. Applicants further submit that a terminal disclaimer may be submitted, in the event that U.S. Serial No. 10/895,646 issues prior to the present application.

Rejections under 35 U.S.C. § 103(a)

Claims 46-53 and 55-61 were rejected for obviousness over Findeis, WO 96/28471, in view of Schenk, WO 99/27944. Applicants respectfully request that this rejection be withdrawn.

First, Applicants note that, as discussed above, the present claims have been amended to specify very particular peptides, consisting of the sequences set forth in the claims. None of the cited references provides any suggestion or motivation to use these specific peptides in the context of the presently claimed methods and compositions.

Turning now to the rejections, the Examiner cites Findeis for teaching that "certain Aβ sequences, in particular KLVFFA and KLVFF… are valuable for their anti-aggregation properties" and that "compounds which interfere with the production of toxic Aβ or APP fragments would be beneficial for *in vivo* treatment of amyloidosis." Schenk is cited for teaching that "effective treatment and/or prophylaxis of amyloid disease means reducing the amount or level of deposited amyloid aggregates and/or inhibiting the formation of amyloid aggregates," and that "the way to prevent or treat a disease associated with amyloid-β plaque deposits in the brain of a patient is to administer fragments of Aβ or analogs thereof to induce an immunogenic response against certain epitopes within β-amyloid."

Based on this, the Examiner concludes at page 7 of the Action that "*the skilled artisan would further recognize that antibodies directed to a fibrillogenic portion of Aβ would be more effective to interfere with amyloid fibril formation and thus inhibit amyloid aggregation than antibodies directed to a non-fibrillogenic region of Aβ.*" The Examiner reiterates the same argument at page 9 by stating that "*the skilled artisan would recognize that antibodies directed to a fibrillogenic portion of Aβ would be more effective than antibodies directed to a non-*

fibrillogenic region of Aβ with regard to interfering with amyloid fibril formation and subsequenctly inhibiting amyloid aggregation." Applicants respectfully disagree for the following reasons.

First, Applicants note that the Examiner's hypothesis that "*antibodies directed to a fibrillogenic portion of Aβ would be more effective than antibodies directed to a non-fibrillogenic region of Aβ*" is not supported by any evidence. To the contrary, one could argue the opposite since, as was stated in the prior Reply, use of a peptide as an antifibrillogenic agent (i.e., the active pharmaceutical entity) involves a totally different mechanism than use of the same peptide for (i) raising antibodies recognizing the peptide (and the corresponding full-length protein) and (ii) "neutralizing" the undesirable activity of the peptide/protein. Therefore, one would not be motivated to use as a vaccine a peptide shown to have beneficial effects in inhibiting amyloid fibril formation, because antibodies raised against such an antifibrillogenic peptide would most likely completely prevent the peptide's beneficial antifibrillogenic activity. Since the Examiner has not provided any evidence that the immunogenic approach would be more effective than the antifibrillogenic approach, Applicants again submit that it would not have been obvious to combine the two opposing technologies set forth in the cited references.

Second, Applicants invite the Examiner to consider the following document: Pike et al., J. Neuroscience, 1993, 13(4), 1676-87 (a copy is enclosed), in combination with the cited reference: Schenk, WO 99/27944. As will be explained below, Applicants respectfully submit that the combined teachings of these two documents are in full contradiction with the Examiner's unsupported position that "*antibodies directed to a fibrillogenic portion of Aβ would be more effective than antibodies directed to a non-fibrillogenic region of Aβ.*"

Throughout the paper, Pike et al. teaches that the Aβ peptide 25-35 (**$A\beta_{25-35}$**) is capable of forming stable aggregates and that both the soluble and aggregated peptides are highly toxic to neuronal cells. More particularly, Applicants refer the Examiner to Table 1 and the penultimate paragraph of page 1678 (showing aggregation), Figure 4 (where $A\beta_{25-35}$ demonstrated a significant reduction in survival of hippocampal cultures), and Figure 8 (where neurons exposed to aggregated $A\beta_{25-35}$ showed a significant level of degeneration). Therefore, according to the Examiner's hypothesis, that peptide would be a perfect candidate for a vaccine, given that Pike et al. demonstrate that the region comprising amino acids 25-35 of Aβ are important for fibrillogenesis and also are highly toxic to neuronal cells.

Interestingly, Schenk has studied the same peptide for vaccine purposes (see Example IV at pages 48-57 of WO 99/27944). However, the results are not those that would be predicted based on the Examiner's hypothesis. Indeed, as shown in Figure 13 and described at page 55, the antibody titer obtained using $A\beta_{25-35}$ (peak of 125) was the lowest among all of the peptides tested (e.g., peak of 94,647 for human $A\beta_{1-42}$ (AN1792). $A\beta_{25-35}$ was also a poor immunogen for stimulating a proliferative T-cell response (Table 5, page 56). Schenk concludes at page 57, line 7, that $A\beta_{25-35}$ has "*poor immunogenicity.*"

Therefore, Applicants have provided strong evidence opposing the Examiner's rationale for rejecting the current claims, by showing that the fact that a region of the Aβ protein is important for fibrillogenesis does not mean that peptides encompassing that region would be effective immunogens for use in vaccination methods. Therefore, the fact that the peptides of Findeis are antifibrillogenic does not mean that they would be predicted to be effective immunogens for use in vaccination methods, such as those of Schenk. Given the differences

discussed above, Applicants again submit that the claimed peptides would not have been obvious in view of the cited references and, thus, request that this rejection be withdrawn.

Applicants further submit that there are additional factors to consider in the preparation of an effective vaccine such as, for example, the presence/selection of an adjuvant, the size of a peptide antigen, conjugation (or not) of the peptide, and the presence/absence of D-amino acids. These are matters for which guidance is provided in the present application, but are not addressed with respect to the presently claimed peptides in the cited references. This provides further evidence for the non-obviousness of the present claims.

In summary, given the differences noted above, Applicants again submit that it would not have been obvious to combine the two opposing technologies set forth in the cited references: (i) the use of antifibrillogenic peptides binding to Aβ and inhibiting fibril formation (Findeis), and (ii) the use of peptides to induce an immune response against Aβ (Schenk). Even if Findeis taught that their peptides were immunogenic (which they did not do), this would not mean that antibodies against these peptides would have antifibrillogenic effects or that such effects (if any) would be greater than that obtained with antibodies against other Aβ peptides. Applicants submits that the Examiner has not establish a prima facie case of obviousness since she has not provided evidence that would indicate that the peptides of Findeis would be sufficiently immunogenic, and that antibodies against these peptides would have the desired effects. To the contrary, the Applicants have provided evidence that the Examiner's position that "*antibodies directed to a fibrillogenic portion of Aβ would be more effective than antibodies directed to a non-fibrillogenic region of Aβ*" is ill-founded because Schenk has shown that at least some of the Examiner's allegedly useful peptides actually have "*poor immunogenicity*". In view of this,

Applicants respectfully request that this rejection be withdrawn.

Claims 46-53 and 55-61 remain rejected for obviousness over Schenk, WO 99/27944; Alberts et al., Molecular Biology of the Cell, 2nd Edition, 1989; and Kalaria et al., Ann. N.Y. Acad. Sci. 893:113-125, 1999; in view of Tjernberg et al., J. Biol. Chem. 271:8545-8548, 1996; Findeis, WO 96/28471; Van Regenmortel et al., Curr. Opin. Biotech. 9:377-382, 1998; Isowa et al., U.S. Patent No. 4,116,768; and Clayberger et al., U.S. Patent No. 6,436,903. This rejection is respectfully traversed.

First, Applicants note that, as discussed above, the claims have been amended to specify very particular peptides, consisting of the sequences set forth in the claims, and none of the cited references provides any suggestion or motivation to use these specific peptides in the context of the presently claimed methods and compositions.

Schenk is cited for teaching the administration of Aβ peptides for the induction of an immune response. Tjernberg and Findeis are cited for teaching Aβ peptides and their use in preventing amyloid fibril formation, with Findeis also being cited for teaching substitutions of all D-amino acids for all L-amino acids in such peptides. Van Regenmortel is cited for teaching that peptides assembled from D-amino acids are more stable to proteolysis than L-peptides, Isowa is cited for teaching the use of amino and carboxyl terminal protective groups for the stabilization of peptide compounds, and Clayberger is cited for teaching immunomodulating peptide compounds including D-amino acids, N-terminal acylated and C-terminal amidated peptides, and the use of modified amino acids such as, for example, phenylglycine.

Applicants refer to the arguments set forth above in response to the prior rejection with respect to the combination of Findeis, Tjernberg, and Schenk. As is stated above, the approaches

of Findeis (and Tjernberg) and Schenk involve inhibition of fibril formation by peptides and use of peptides as vaccine antigens, respectively, and these approaches involve completely different and contradictory mechanisms.

Further, as is stated above, the fact that the peptides of Findeis (or Tjernberg) are antifibrillogenic does not mean that they would be predicted to be effective immunogens for use in vaccination methods, such as those of Schenk. Evidence supporting this statement is provided by the Pike reference (see above) and the cited Schenk reference. As discussed above, Pike showed that certain sequences are important for fibrillogenesis, and Schenk showed that a peptide including these sequences was poorly immunogenic. Further, even if Findeis (or Tjernberg) taught that such peptides were immunogenic (which Findeis and Tjernberg did not do), this would not mean that antibodies against the peptides of Findeis (or Tjernberg) would have antifibrillogenic effects or that such effects (if any) would be greater than that obtained against other Aβ peptides. No evidence has been provided that would indicate that the peptides of Findeis (or Tjernberg) would be sufficiently immunogenic, and that antibodies against these peptides would have the desired effects. In view of this, Applicants respectfully request that the rejection be withdrawn.

The references describing, e.g., increased stability of peptides including [D]-amino acids, terminal modifications, and/or conservative substitutions do not provide any information that overcomes this fundamental problem with this rejection, which Applicants thus request be withdrawn.

Applicants further note that Schenk does not teach sequences consisting entirely of [D]-amino acids, and there is no suggestion or motivation in the art that would indicate that such

peptides would have the beneficial effects of the presently claimed peptides. Thus, the claimed immunogenic peptides, comprising the KLVF sequence made exclusively of [D]-amino acids, are an unexpected selection over the various peptides fragments suggested by Schenk and others. As discussed above, the present claims now focus on very specific, novel, and non-obvious peptides. This rejection should therefore be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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